Methods: The distal superficial femoral arteries of rabbits were ligated, the ligatures were removed at 24 or 48 hours, urokinase (10,000 U/kg) was given intravenously, and the vessels were harvested at 2 weeks. Control vessels were dissected but not ligated. Intimal and medial areas were quantified with computer image analysis of Verhoff-von Geisen stained sections.

Results: Complete clot lysis with urokinase was documented histologically following 48 hour occlusion (n = 4) harvested 24 hours after thrombolysis. Mean intima to media ratios were 0.043 ± 0.002 SE (n = 5) for control, 0.072 ± 0.012 (n = 5, p = 0.37 vs. control) for 24 hour and 0.183 ± 0.033 (n = 6, p = 0.0004 vs. control, p < 0.003 vs. 24 hour vessels) for 48 hour thrombosed/reperfused vessels. Histologic analysis with specific monoclonal antibodies demonstrated that the neointima of reperfused vessels were densely infiltrated with α-actin positive cells.

Conclusion: Prolonged thrombosis (>24 hours), even after successful reperfusion, induces intimal thickening. These results provide a novel mechanism for the high incidence of restenosis after reperfusion of chronically occluded arteries.

1115 Myocardial Function

Tuesday, March 31, 1998, Noon–2:00 p.m.
Georgia World Congress Center, West Exhibit Hall Level
Presentation Hour: Noon–1:00 p.m.

1115-11 FR167653, a Cytokine Suppressive Agent, Reduces Myocardial Ischemia-Reperfusion Injury in Rats

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Background: FR167653 is a specific inhibitor of p38 MAP kinase activity and inhibits the production of inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) in human monocytes in a dose dependent manner (IC50, TNF-α: 1.1 μM, IL-1β: 0.088 μM).

Methods: We examined the effect of FR167653 on the propagation of myocardial infarction resulting from coronary occlusion-reperfusion and the time course of expression of these cytokines in myocardial tissue in rats. Myocardial infarction was induced by coronary ligation for 20 minutes followed by 24 hours of reperfusion. Infarct size was evaluated by a dual staining method using TTC and Evans blue dye.

Results: Although hemodynamic parameters did not differ significantly during occlusion-reperfusion, the size of the infarct was reduced by intravenous administration of FR167653 before occlusion (control: 46 ± 2%; FR 1 μg/kg: 19 ± 2%; 10 μg/kg: 17 ± 2%, p < 0.05). mRNA of these cytokines assessed by RT-PCR was significantly increased during occlusion and reperfusion in ischemic myocardium (indicated as TNF-α or IL-1β/G3DPH, TNF-α: before occlusion 0.38 ± 0.09, 20-minute occlusion 0.77 ± 0.13, 60-minute reperfusion 1.49 ± 0.16, p < 0.05 respectively; IL-1β: before occlusion 0.09 ± 0.02, 20-minute occlusion 0.31 ± 0.03, 60-minute reperfusion 0.34 ± 0.04, p < 0.05 respectively). However, FR167653 significantly reduced the expression of these cytokines (TNF-α: 20-minute occlusion 0.49 ± 0.05, 60-minute reperfusion 0.72 ± 0.18; IL-1β: 20-minute occlusion 0.03 ± 0.01, 60-minute reperfusion 0.09 ± 0.03).

Conclusion: The expression of inflammatory cytokines increases in ischemic/reperfused myocardium and the inhibition of the augmented expression of cytokines by FR167653 effectively reduces myocardial ischemia-reperfusion injury.

1115-12 Effects of ORG 30029, Dobutamine, and High Perfusate Calcium on Function and Metabolism in Rat Heart

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Background: ORG 30029 (N-hydroxy-5 6-dimethoxy-benzo [b] thiophene-2-carboximidamide HCl) is a calcium sensitizing agent that increases contractility without significantly altering calcium transient amplitude. The purpose of this study was to compare the effects of ORG 30029 on cardiac function and metabolism to that of high perfusate calcium and dobutamine; which increase calcium transients.

Methods: Isovolumic, Langendorff-perfused rat hearts were paced (5 Hz) while oxygen consumption (MVO_2, mcmol/min/gm), high energy phosphates by ^{31}P NMR, lactate production, and force-time integral (FTI, dynes·secs) were measured during control and agents. Effects on basal metabolism were determined in KCl-arrested hearts.

Results: Each agent increased contractility in a dose-dependent manner. Despite an increase of 50% in systolic pressure and a 17% in FTI from control, ORG 30029 had no significant effect on MVO_2 at the lower doses (n = 12). However, dobutamine (n = 7) and high perfusate calcium (n = 7) caused a 65% increase in systolic pressure and a 17% increase in FTI and a 50% and 41% in MVO_2, respectively (p < 0.05). Contractile economy (FTI/MVO_2) was increased by ORG 30029, decreased by dobutamine, and unaffected by high perfusate calcium compared to control (p < 0.05). High energy phosphates, lactate production, and basal metabolism were unaltered by these agents.

Conclusion: The different energetic effects of ORG 30029, dobutamine, and high perfusate calcium may be accounted for, in part, by differences in energy for calcium handling.

1115-13 Effects of Intravenous Amiodarone on Ventricular Vulnerability: An Optical Imaging Study in Isolated Rabbit Hearts

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Background: Intravenous amiodarone (Am) is being considered for incorporation into protocols for advanced cardiac life support in the treatment of ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT). We studied Am effects on ventricular vulnerability in six Langendorff-perfused rabbit hearts.

Methods: High-speed optical imaging was utilized, without uncoupling agents, to observe wavefront dynamics during and after shock (S2) application through internal leads in the pulmonary artery and left ventricular apex. A monophasic 5 ms S2 of various strengths was applied at different coupling intervals after 20 driving stimuli. The ventricular vulnerable period (VVP) and the upper limit of ventricular vulnerability (ULV) were determined before and after addition of Am at 1.5 mg/ml. The action potential duration (APD_{90}) was also measured at pacing cycle lengths of 500 ms and 350 ms.

Results: Am did not induce significant change in APD_{90} during 500 ms pacing (137.7 ± 4.7 ms → 142.8 ± 1.6 ms, p = NS). However, during pacing at 350 ms, Am significantly increased APD_{90} (111.8 ± 6.2 ms → 134.0 ± 6.5 ms, p < 0.05). Am also shifted the mid-point of VVP to the right (160.0 ± 11.5 ms → 195.0 ± 25.2 ms, p < 0.05). Furthermore, Am significantly increased ULV (162.5 ± 77.7 V → 212.5 ± 32.3 V, p < 0.05). After Am treatment, arrhythmic wavefronts propagated more slowly and were organized into regular VT (5/6 hearts). The dominant arrhythmia cycle length increased significantly after drug treatment (96.5 ± 15.9 ms → 132.8 ± 17.2 ms, p < 0.05).

Conclusion: Am-induced preferential prolongation of APD at short cycle length may be the primary mechanism responsible for its reduction in VF inducibility and the increased arrhythmic wavefront stability. Whether the associated increase in ULV indicates an increase in the defibrillation threshold needs further study.

1115-14 Beneficial Effects During Ischemia-Reperfusion: Synergistic Action of Levosimendan and Dobutamine

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Levosimendan (Levo), a novel Ca^{2+}-sensitizing agent, has not been used in acute ischemic syndromes. We hypothesized that Ca^{2+}-sensitizers, like Levo, may overcome acute ischemic pump failure, therefore we tested whether Levo alone or with dobutamine (Dob) could improve ischemic contractile failure without increasing diastolic dysfunction during ischemia and reperfusion (Isch + Rep). Isolated, blood perfused, isovolumic rabbit hearts were subjected to 40' Isch by reducing coronary flow to → 25% of baseline, followed by 35' Rep. Four groups (n = 6–8/group) were studied: saline (S), Levo (0.4 μM), Dob (5 μM) and Levo + Dob. Surprisingly, Levo alone had no effect on systolic or diastolic function, but caused coronary vasodilatation during Isch (coronary perfusion pressure at 40' Isch: 18 ± 1 vs. 21 ± 1 mmHg; Levo vs. S; p < 0.05) and at 15' Rep (42 ± 2 vs. 86 ± 9 mmHg; Levo vs. S, p < 0.001). Dob alone worsened diastolic dysfunction which was improved by Levo + Dob (LVEDP at 35' Rep: 25 ± 5 vs. 14 ± 3 mmHg, Dob vs. Levo + Dob; p < 0.001). Levo + Dob and Dob exerted a positive inotropic effect during ischemia (LV developed pressure (LV DevP) at 40' Isch: 72 ± 4 and 68 ± 2 vs. 51 ± 4 mm Hg; p < 0.001 vs. S). During Isch, MVO_2 was unaffected by Levo but increased with Dob (12%) and Levo + Dob (17%) (p < 0.001 vs. S). % recovery of LV DevP at 15' Rep was further increased in Levo + Dob compared to Dob alone (106 ± 7 vs. 89 ± 3%; p < 0.001).

Conclusion: During Isch + Rep, levosimendan in combination with dobutamine had a positive inotropic effect that surpassed that of dobutamine alone and ameliorated post-ischemic diastolic dysfunction. This combination may be clinically useful in acute ischemic syndromes.